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Total colonic Hirschsprung's disease and anorectal malformation in a baby with Pallister–Hall syndrome

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ABSTRACT

Pallister Hall syndrome (PHS) is a rare polymorphic syndrome of autosomal dominant inheritance characterized by the coexixtance of an hypotalamic hamartoma and polydactyly. Anorectal malformations are commonly present in patients with PHS. Hirschsprung's disease can exist in isolation or associated with a variety of genetic syndromes. In the current report, we present a patient with PHS, anorectal malformation and total colonic Hirschsprung's disease.

Pallister–Hall syndrome (PHS) is a polymorphic syndrome of autosomal dominant inheritance with a wide range of severity. It was initially described in 1980 in six infants with, at that time, an unknown neonatal lethal syndrome [1]. The key clinical components are hypothalamic hamartoma and polydactyly. Patients with PHS frequently have malformations of the kidneys, heart, airway and genitourinary system. Additionally, anorectal malformations are present in most patients with PHS. Hirschsprung's disease is a congenital anomaly of the enteric nervous system characterized by the absence of ganglion cells in the intestinal wall. Patients may fail to pass meconium, develop intestinal obstruction or constipation, and invariably require resection of the aganglionic segment of intestine. Hirschsprung's disease can exist in isolation or associated with a variety of syndromes such as trisomy 21, Waardenburg–Shah syndrome, and piebaldism [2]. The association of PHS and an anorectal malformation with Hirschsprung's disease is rare and has only been formally reported once in the literature [3]. In the current report, we present a case of a neonate with the diagnosis of PHS and an anorectal malformation who also had total colonic Hirschsprung's disease. We performed an extensive review of the literature which identified the one known reported case and three other cases of PHS associated with Hirschsprung's disease and anorectal malformation that were published before Pallister–Hall was established as a syndrome [1,3,4]. This literature review is presented in the context of the clinical details of our case which is the first report of total colonic Hirschsprung's disease associated with an anorectal malformation and PHS.

1. Case report

A 30-year-old primigravida with no significant past medical history was referred to us at 28 weeks gestation due to multiple fetal abnormal findings found on prenatal ultrasound. Fetal echocardiogram, maternal-fetal ultrasound, and ultrafast fetal magnetic resonance imaging revealed polyhydramnios, hypothalamic hamartoma, low conus medullaris (L4), maxillary and mandibular hypoplasia, hypoplastic and heterogenous kidneys without cortico-medullary differentiation, abnormal perineum without visualization of the anal dimple, ambiguous genitalia, microphallus, undescended testes, and post axial polysyndactyly on both hands. Amniocentesis revealed a normal male-type chromosome set (46, XY) and a disease-causing mutation in exon 15 of the GLI3 gene, confirming the suspected diagnosis of PHS. Non-directional counseling was given to the parents and despite the poor prognosis they elected to continue the pregnancy. The baby was born at 37 weeks of gestation, weighed 2.9 kg, and required intubation at 20 min of life due to respiratory distress. The anus was imperforate and there were no external signs of a rectal fistula. He

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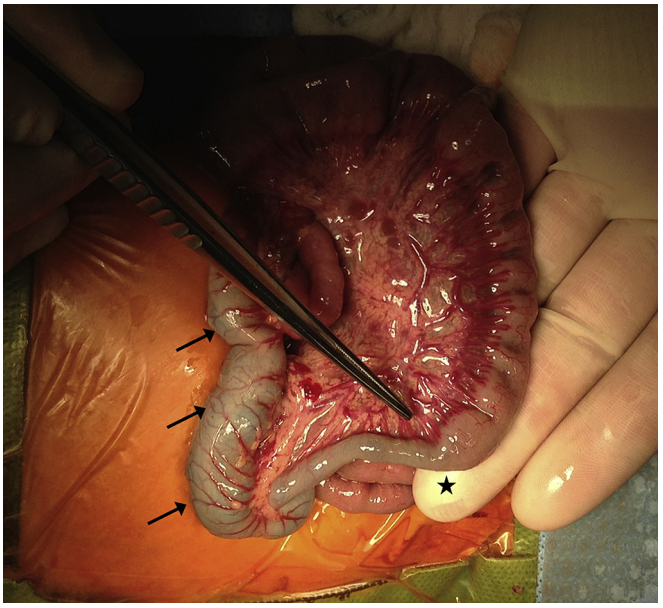

Fig. 1. Narrowing area at the distal ileum 5 cm proximal to the ileocecal valve (star). The ascending colon has a normal caliber (arrows).

developed hypoglycemia and hypotension within the first 24 h of life that responded to steroid therapy. Panhypopituitarism was confirmed within the first few days of life (low FSH, LH, GH, and T4). On day of life (DOL) 2 a laryngoscopy/bronchoscopy was performed and showed bilateral choanal atresia, bifid epiglottis, type 2 laryngeal cleft, complete tracheal rings, and a pig bronchus (right upper lobe bronchus arising from the trachea). Also on DOL 2 he underwent a diverting sigmoid colostomy. The sigmoid colon was normal in caliber. Postoperatively, he had minimal output from his colostomy and failed to have bowel function. This was initially thought to be secondary to the electrolyte derangements (hyperpotassemia and hyponatremia) associated to his adrenal and renal insufficiency. A retrograde contrast study through the colostomy was done 4 weeks postoperatively and showed an area of narrowing in the distal ileum (Fig. 1). At laparotomy, an ileal stenosis was found 5 cm proximal to the ileocecal valve and an ileocecectomy with ileocolic primary anastomosis was done. Pathology showed aganglionosis throughout the ileocecectomy specimen, with ganglion cells only present in the ileum proximal to the stenosis. The patient was taken back to the operating room, total colonic Hirschsprung's disease was confirmed by intraoperative frozen section biopsies, and a terminal ileostomy at the most distal ganglionated segment was performed. The baby's clinical condition gradually worsened. He was unable to be weaned from the ventilator, developed refractory hypertension and repeated episodes of unexplained bradycardia. Due to his multiple medical issues and failure to improve the parents decided to withdraw care at the age of 3 months. A distal colostogram to delineate the anatomy of the anorectal malformation was never done. The family declined an autopsy.

2. Discussion

PHS is caused by truncation mutations in the GLI3 gene that are inherited in an autosomal dominant manner. About 75% of the cases are hereditary whereas 25% occur due to de novo mutations. The GLI3 gene is located at the 7p13 locus and encodes a zinc finger transcription factor that regulates the sonic hedgehog (Shh) pathway [5]. Early prenatal diagnosis of PHS syndrome is possible by genetic analysis of fetal cells collected by amniocentesis or chorionic villous sampling. Testing is indicated in fetuses of families with prior probands and fetuses without a family history but with suspicious anatomical features such as a hypothalamic tumor and polydactyly on prenatal imaging studies.

The clinical presentation of PHS is widely variable and few cases result in neonatal death. Mortality is related to major airway malformations or severe panhypopituitarism. Most patients with PHS have some form of anorectal malformation, which should be managed with the same therapeutic algorithms applied to anorectal malformations in non-PHS patients. The unrecognized coexistence of Hirschsprung's disease can lead to disastrous consequences following the correction of the anorectal malformation. Patients who undergo a colostomy at an aganglionic segment as the initial management of the anorectal malformation (as in the current case) will fail to resume bowel function. This should alert about the possibility of Hirschsprung's disease. Patients who undergo a colostomy proximal to the aganglionic segment will remain undiagnosed until after the anorectoplasty and subsequent colostomy closure. These patients will require a repeat anorectoplasty, which has detrimental effects on the function of the anorectal muscle complex [6]. Patients with anorectal malformations are not routinely screened for Hirschsprung's disease because the coexistence of both conditions in the general population is exceedingly rare [7]. An important distinction must be made between true Hirschsprung's disease and the lack or paucity of ganglion cells that is always observed in the most distal segment of bowel of any type of anorectal malformation. Peña et al. reported that in their series of more than 7000 patients with anorectal malformations only 3 (0.04%) were found to have Hirschsprung's disease [8]. It appears, however, that the incidence of this combination might be higher in syndromic patients (e.g.

Table 1
Cases of anorectal malformations and Hirschsprung's disease in patients with Pallister–Hall syndrome.

	Case 1	Case 2	Case 3	Case 4	Case 5
Author	Healy et al. [4]	Hall et al. [1]	Hall et al. [1]	Haynes et al. [3]	Current case
Gender	Male	Male	Female	Male	Male
Anorectal malformation	Yes	Yes	Yes	Yes	Yes
Type of anorectal malformation	Anal atresia without fistula	Anal atresia without fistula	Recto-vaginal fistula	Rectourethral fistula	[c]
Hirschsprung's disease	Yes	Yes	Yes	Yes	Yes
Extension of aganglionosis	N/A	Mid-transverse colon	Descending colon	Descending colon	Total colonic aganglionosis
Polydactyly	Yes	Yes	Yes	Yes	Yes
Hypothalamic hamartoma	[a]	Yes	[b]	Yes	Yes
Bifid epiglottis	Yes	No	N/A	N/A	Yes

N/A = no data available.
[a] This patient was born in 1960; no images of the brain were done.
[b] No autopsy was done but the patient had clinical hypopituitarism, most likely from a hypothalamic hamartoma.
[c] Patient's anus was imperforate, but a formal distal colostogram to determine the presence and location of a rectal fistula was never done.

Down's syndrome) and patients with other malformations such as intestinal malrotation [9–16]. In fact, a literature review demonstrated 4 cases of anorectal malformation plus Hirschsprung's disease in patients with PHS (Table 1). The diagnosis of Hirschsprung's disease was made postmortem in 2 cases, at 8 weeks in one case (failure to pass stool after anoplasty) and at 13 months in one case (dehiscence of the colostomy take-down). Our patient is the first with PHS and *total colonic* Hirschsprung's disease, which was diagnosed at 8 weeks of age.

PHS is a rare disorder and even rarer is the coexistence of PHS, anorectal malformation and Hirschsprung's disease. In light of our case and the cases found in the literature, however, we suggest that exclusion of Hirschsprung's disease should be considered in all patients with PHS and anorectal malformation prior to any definitive anorectoplasty.

Conflict of interest statement

None of the authors have any conflicts of interest to declare.

References

[1] Hall JG, Pallister PD, Clarren SK, Beckwith JB, Wiglesworth FW, Fraser FC, et al. Congenital hypothalamic hamartoblastoma, hypopituitarism, imperforate anus and postaxial polydactyly – a new syndrome? Part I: clinical, causal, and pathogenetic considerations. Am J Med Genet 1980;7:47–74.
[2] Langer JC. Hirschsprung disease. In: Coran AG, Adzick NS, Krummel TM, Laberge JM, Shamberger R, Caldamone A, editors. Pediatric surgery. 7th ed. Philadelphia, PA: Elsevier; 2012. p. 1265–78.
[3] Haynes JH, Bagwell CE. Hirschprung's disease and imperforate anus in Pallister-Hall syndrome: a new association. J Pediatr Surg 2003;38:1411–2.
[4] Healy GB, Holt GP, Tucker JA. Bifid epiglottis: a rare laryngeal anomaly. Laryngoscope 1976;86:1459–68.
[5] Motoyama J. Essential roles of Gli3 and sonic hedgehog in pattern formation and developmental anomalies caused by their dysfunction. Congenit Anom (Kyoto) 2006;46:123–8.
[6] Peña A, Hong AR, Midulla P, Levitt M. Reoperative surgery for anorectal anomalies. Semin Pediatr Surg 2003;12:118–23.
[7] Raboei EH. Patients with anorectal malformation and Hirschsprung's disease. Eur J Pediatr Surg 2009;19:325–7.
[8] Peña A, Levitt M. Comments on Hirschsprung's disease as presented by Arbell et al. J Pediatr Surg 2006;41:1942–3.
[9] Flageole H, Fecteau A, Laberge JM, Guttman FM. Hirschsprung's disease, imperforate anus, and Down's syndrome: a case report. J Pediatr Surg 1996;31:759–60.
[10] Clarke SA, Van der Avoirt A. Imperforate anus, Hirschsprung's disease, and trisomy 21: a rare combination. J Pediatr Surg 1999;34:1874.
[11] Luo CC, Ming YC, Chu SM, Chao HC. Rare association of malrotation, imperforate anus and Hirschsprung's disease in an infant. Pediatr Int 2010;52:e9–10.
[12] Oshio T. Imperforate anus, malrotation, and Hirschsprung's disease with double zonal aganglionosis: an extremely rare combination. J Pediatr Surg 2008;43:222–6.
[13] Poenaru D, Uroz-Tristán J, Leclerc S, Murphy S, Bensoussan AL. Imperforate anus, malrotation and Hirschsprung's disease: a rare association. Eur J Pediatr Surg 1995;5:187–9.
[14] Mahboubi S, Templeton Jr JM. Association of Hirschsprung's disease and imperforate anus in a patient with "cat-eye" syndrome. A report of one case and review of the literature. Pediatr Radiol 1984;14:441–2.
[15] Sinha CK, Grewal A, Ward HC. Short-segment Hirschsprung's disease, cat eye syndrome, and anorectal malformation: a unique association. J Pediatr Surg 2007;42:1454–6.
[16] Ohno K, Nakamura T, Azuma T, Nakaoka T, Takama Y, Hayashi H, et al. Familial Currarino syndrome associated with Hirschsprung disease: two cases of a mother and daughter. J Pediatr Surg 2013;48:233–8.